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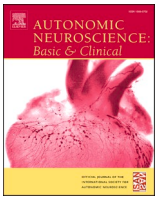

The pathophysiology of vasovagal syncope: Novel insights

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A B S T R A C T

The pathophysiology of vasovagal syncope (VVS) is reviewed, focusing on hemodynamic aspects. Much more is known about orthostatic than about emotional VVS, probably because the former can be studied using a tilt table test (TTT). Recent advances made it possible to quantify the relative contributions of the three factors that control blood pressure: heart rate (HR), stroke volume (SV) and total peripheral resistance (TPR). Orthostatic VVS starts with venous pooling, reflected in a decrease of SV. This is followed by cardioinhibition (CI), which is a decrease of HR that accelerates the ongoing decrease of BP, making the start of CI a literal as well as fundamental turning point.

The role of hormonal and other humoral factors, respiration and of psychological influences is reviewed in short, leading to the conclusion that a multidisciplinary approach to the study of the pathophysiology of VVS may yield new insights.

1. Introduction and normal blood pressure physiology

1.1. Scope of this chapter

Vasovagal syncope (VVS) is the most common form of Transient Loss of Consciousness: about one third of all people have at least one VVS spell in their lifetime (Brignole et al., 2018a), and 5% of all people have at least five VVS spells during their lifetime (Thijs et al., 2006). VVS has a negative impact on quality of life and is associated with psychological distress (Ng et al., 2019). In spite of these dual features of being very common and having negative consequences, the mechanisms behind VVS are still imperfectly known. This chapter discusses several aspects of the pathophysiology of VVS with a focus on hemodynamic events, as these are central to VVS. The loss of consciousness (LOC) in VVS is, as in any form of syncope, the result of cerebral hypoperfusion caused by low arterial blood pressure (BP).

We also reviewed other pathophysiological fields, with the intention of identifying other factors that may contribute to the understanding of the pathophysiology of VVS. We excluded the genetics of VVS, as these are discussed in another paper.

In the ESC classification (Brignole et al., 2018a), VVS is a form of ‘reflex syncope’, a category also known under the synonym ‘neurally mediated syncope’. The reflex in question is mediated by the autonomic nervous system. As the neural pathways of VVS are interwoven with the pathways of normal blood pressure (BP) control, the discussion of VVS will be preceded by a brief discussion of the baroreflex, the mainstay of BP control, and a discussion how hemodynamic measurements can be used to infer pathophysiological processes.

1.2. Normal blood pressure regulation

The baroreflex is constantly active and responds to any alteration of BP, either a decrease or increase. The circulatory response to standing up is a well-known example of baroreflex control: because blood tends to gravitate downwards, the volume of blood flowing back to the heart (the ‘venous return’) diminishes, so volume pumped out by the heart (the ‘cardiac output’) decreases likewise, and arterial BP will start to fall. This is sensed by receptors in the carotid sinus and in the aorta, with the aortic ones sensitive to lower pressure than the carotid ones (Lau et al., 2016). The receptors send afferent impulses to the central nervous system, where a response is orchestrated. The resulting efferent impulses descend through dual sympathetic and parasympathetic pathways to the effector organs.

When the baroreflex is triggered by hypotension, the parasympathetic response consists of a decrease of vagal drive to the heart that increases heart rate (HR) (Fig. 1). This will increase cardiac output (CO), driving more blood into the arteries. The sympathetic response results in an increase in activity to the heart that also increases HR, as well as an increase of impulses to arterioles that result in more vasoconstriction, increasing total peripheral resistance (TPR), thereby impeding blood flowing out of the arteries. The dual effects of driving more blood into the arteries while impeding blood flowing out them increase arterial BP (Fig. 1). An initial disturbance in the form of a BP increase will have opposite effects on HR and TPR, so BP will decrease. A

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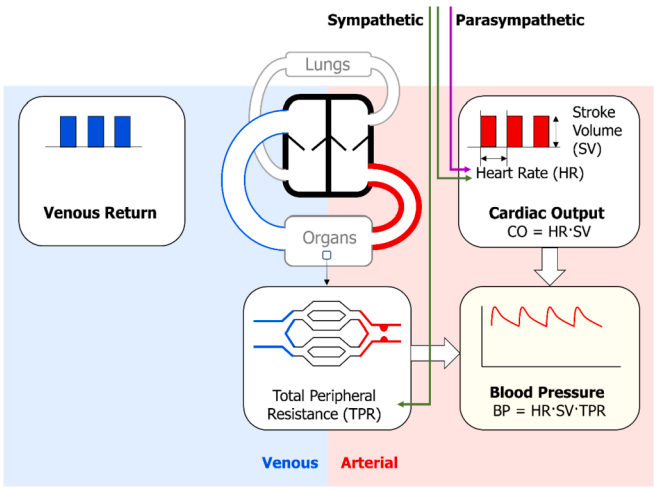

Fig. 1. Schematic view of the circulation.
The circulation is drawn with a focus on the arterial part of the circulation. The autonomic control over blood pressure (BP) is exerted through descending parasympathetic influence over heart rate (HR), and sympathetic influences on HR and total peripheral resistance (TPR). These autonomic influences can lower as well as increase HR and TPR.
The volume the heart pumps out per beat is the stroke volume (SV). The product of HR and SV is the volume pumped out by the heart into the arteries during 1 min: the cardiac output (CO). TPR impedes the flow of blood out of the arteries, and is enacted by sympathetically controlled vasoconstriction in arterioles. The product of TPR and CO is BP, shown here as the typical oscillation observed with continuous BP measurements. Under normal stable circumstances, the volume of blood returning to the heart, venous return, is per minute the same as CO.

fundamental feature of baroreflex control is the reciprocal relation between changes of BP and HR: BP decreases are normally accompanied by HR increases, and vice versa.

1.3. Disentangling hemodynamic influences

Although Ohm's law was designed to describe the relations between electrical current, voltage and resistance, there is an analogue that describes the flow of fluids through conduits, such as the circulation. Here, the arterial system shall be the conduit (Fig. 1). Current is analogous to blood flow, here CO, in liters per minute. Voltage is analogous to the pressure that drives flow, which is arterial BP (or, more precisely, the pressure difference between the left ventricle and ultimately the right atrium). Finally, electrical resistance is the analogue of the resistance posed by the arterioles where active vasoconstriction takes place, in other words, TPR:

$$CO = \frac{BP}{TPR}$$

This equation can be rearranged to yield: BP = CO·TPR. As CO is the product of HR and SV, the equation becomes:

$$BP = HR \cdot SV \cdot TPR$$

BP is therefore the product of three hemodynamic parameters. Changes in BP at any given time can be assigned with confidence to a specific mechanism only if all three parameters are known for that time. The principle is that a BP decrease at some point in time must be due to whichever of the parameters HR, SV and TPR decreased at that time. If any of the three in contrast increased at that time, that one cannot have caused low BP. Instead, the increase must be due to one of two other explanations: the increase could be the result of a compensatory effort to limit the BP decrease, or it is a direct mechanical consequence of the decrease of another parameter. Two examples may help understand the reasoning:

- If BP decreases slowly, while HR rises, SV decreases, and TPR stays the same, then low SV is the cause of low BP, with a corrective effort by HR and no role for TPR.
- If a sudden BP decrease is accompanied by an abrupt lowering of HR, an increase of SV and no change of TPR, then low BP can be attributed to low HR; the rise in SV probably reflects augmented filling of the left ventricle during prolonged diastole.

Three aspects regarding the application of the equation should be kept in mind. Firstly, the equation describes a momentary state and should not be used to predict BP alterations. In other words, it should not be assumed that, if one parameter changes, the other parameters will stay the same. The others may well respond to the primary change over time. For example, doubling HR, by pacing, is not likely to exactly double BP: the higher HR decreases the filling time of the heart, and that will lower SV, partially negating the HR effect. The intricate relation between HR and SV means that changes are not easy to predict. When HR, BP and CO are all in low normal ranges, increases of HR are likely to increase CO; however, above around 125 bpm, increasing HR may well result in a net decrease of CO, in VVS and other conditions (Stewart et al., 2020).

Secondly, there is at present no method to directly measure all the parameters BP, CO, HR, SV and TPR (Izzo et al., 2019). HR and BP can be measured easily and reliably. Some assessment methods measure CO and use that to calculate SV, while others, such as Modelflow, use a measure of SV to calculate CO. All methods rely on calculations to obtain a value for TPR, using the relation between CO, BP and TPR. As TPR lies at the end of a chain of calculations, it is probably most prone to error.

Thirdly, the interpretation needs caution. In some cases, autonomic nervous influences may be deduced safely: when HR changes within one or two heart beats, the cause probably lies in vagal influences. But in many other cases, in particular longer lasting changes, the influence of autonomic as well as hormones and other humoral factors should be considered.

1.4. VVS as a reflex

The reflex pathways of VVS differ in at least two cardinal ways from normal baroreceptor-driven BP control.

Firstly, the VVS process causes arterial hypotension; if hypotension is to be explained as the product of a regulatory reflex, the expected disturbance setting that reflex in motion should be hypertension, or at least some function associated with hypertension. This is obviously not the case in VVS; two possible explanations come to mind to explain the discrepancy. One is that the reflex response is out of control and completely inappropriate to the original disturbance. The second is that the reflex response is in fact adequate, which supposes that there is a problem that is solved by shutting down the circulation and thereby the brain. This possibility supposes that VVS, a uniquely human response, has an evolutionary benefit. Whether this is so has not been settled, due to a lack of evidence. Hypotheses include that VVS protects the body against hemorrhage, against human assailants, or that VVS protects the heart (van Dijk and Sheldon, 2008; Alboni and Alboni, 2017). A recent finding pointed towards the existence of a specific adrenoreceptor subtype that is both tied to human evolution and to VVS; if substantiated, this relation favors an adaptive role for VVS (Komiyama et al., 2015).

The second cardinal difference from normal baroreceptor control is that BP and HR decrease together in most forms of reflex syncope and definitely in the final stages of VVS (see Section 2.2.3). The reversal of the usual reciprocal behavior means that normal baroreceptor control is lost during VVS (Ogoh et al., 2004) or overridden by a stronger command.

1.5. Afferent pathways: central/emotional versus peripheral/orthostatic

Efferent activity can be measured, using means such as measuring

nerve traffic in sympathetic nerve bundles to blood vessels in muscles, or dissecting hemodynamic parameters such as HR, TPR and SV using noninvasive continuous blood pressure monitoring devices. Unfortunately, neither sensor activity nor neural afferent responses can be monitored with ease, so afferent pathways in VVS are much less clear than efferent ones.

Knowledge of afferent paths of necessity relies on inferences made from the triggers. VVS is commonly triggered by pain, fear and prolonged standing (Brignole et al., 2018a), but the chances of VVS occurring are influenced by a host of factors, such as stopping with running, resting after a heavy meal, not drinking enough, fever, a hot environment, crowding, as well as less quantifiable circumstances such as long-term anxiety. Some factors may have a circulatory change in common, such as a lowering of blood pressure, or a reduction or redistribution of the circulating volume. Others may well rely on pain afferents. Emotional triggers stand apart from all other triggers in that they can cause VVS purely by transferring cognitive information, for instance talking about someone else's surgery. Oddly, the human circulation can come to a standstill after the reception of relatively innocent information. We will label such fear-related triggers, including pain, as 'emotional'. The afferent pathway of emotional VVS is largely unknown. The final phase of the efferent path of emotional VVS obviously comprises low BP with or without low HR, and is therefore known, but the events preceding that final pathway are unknown. We know of no test protocol that evokes pure emotional VVS.

Knowledge of the pathophysiology of VVS almost exclusively rests on tilt table testing (TTT) and similar techniques such as lower body negative pressure, implying or mimicking a gravitational challenge. When patients with emotional VVS develop VVS during TTT, the result does not appear fundamentally different from that in those with orthostatic VVS. Still, this does not mean that the pathways of emotional and orthostatic VVS must be the same. TTT may evoke fear as well as providing an orthostatic challenge, and it is also possible that the VVS pathways that are primarily activated by TTT are only orthostatic ones.

2. Hemodynamics of vasovagal syncope

2.1. Setting the background

2.1.1. Classical views of VVS

The history of pathophysiological understanding of VVS was reviewed in two papers (Wieling et al., 2016; Jardine et al., 2018). Early views on VVS held that vasodilatation was the main cause of low BP; as this was deduced from TPR measurements, *arterial* vasodilatation was meant. The efferent pathway was seen as a combination of decreased arteriolar vasoconstriction (low TPR) and vagal bradycardia (low HR). However, later studies found cardiac output (CO) to decrease well before syncope and well before any significant arteriolar vasodilatation, if that occurred at all. Low CO was due to a decrease of SV, attributed to reduced venous return, itself attributed to venous blood pooling, in the splanchnic or muscular veins. Note that venous pooling also implies vasodilatation, but of veins; to prevent confusion, we will systematically differentiate between venous and arterial vasodilatation.

2.1.2. Vasodepression and cardioinhibition

The concept 'vasodepression' (VD) was used in some papers as a release of vasoconstriction in arterioles only (low TPR), while other sources (Brignole et al., 2000) did not stipulate a specific site or mechanism. We will present arguments in Section 2.2.2 to widen the meaning of VD to encompass both venous and arterial vasodilatation.

Cardioinhibition was pragmatically defined in the VASIS context to describe TTT patterns. The 'VASIS 2A' pattern concerns bradycardia without asystole, with bradycardia defined as HR being less than 40 bpm during at least 10 s, and asystole as a pause of at least 3 s. When asystole occurred, events were classified as 'VASIS 2B' (Brignole et al., 2000). These standardized abnormality thresholds for bradycardia and asystole have proven very useful to promote consistency in VVS research. However, they are not associated with specific pathophysiological consequences for BP or for brain perfusion, so their occurrence does not point to a specific BP or a specific level of brain perfusion.

How quickly asystole can cause loss of consciousness (LOC) can be extracted from arrhythmias, in which asystole starts without the confounding influences of vasodepression. Based on older sources that are difficult to falsify, a review reported loss of consciousness to start as early as 4–8 s after the last beat in standing subjects, and 12–15 s if they were lying down. (Wieling et al., 2009). Note that asystolic periods of 3 s need not even be perceived by patients. Asystole in VVS attracted a great deal of attention because it could in principle be remedied with cardiac pacing, a subject largely outside the subject of this chapter. Asystole is an extreme expression of CI and often follows less severe bradycardia, showing that CI encompasses more than just asystole.

2.2. Novel insights

2.2.1. 'Low blood pressure phenotype'

The 2018 ESC guidelines coined the concept 'low BP phenotype' to indicate a susceptibility to VVS. While the concept was based on clinical experience, in that factors that contribute to low BP, such as dehydration and little water or salt intake, increase the chances of VVS, it was not formally proven. A multicohort cross-sectional study changed this, using resting BP measurements (Brignole et al., 2021). Diastolic BP (DBP) and HR were higher in VVS populations than in the general population in both sexes and systolic BP (SBP) was lower in men, but not in women. The differences were not large (3–5 mmHg for DBP and 5 bpm for HR) but highly significant. The hemodynamic state of VVS patients therefore differed in the resting state from that of healthy controls, and the pattern might be more accurately described as 'low systolic BP phenotype'. The pattern, with low SBP, high DBP, and therefore a low pulse pressure, was compatible with reduced venous return and low SV. The authors proposed several explanations: an overall low circulating volume or a redistribution of blood, a low BP setpoint, and a different neuroendocrinological state. Finally, VVS patients showed a lower-than-expected increase of BP with age, a finding that may underlie the upper half of the bimodal age distribution of VVS.

The 'low BP phenotype' may tie in with another novel concept, that of 'hypotensive susceptibility' in the TTT context (Sutton and Brignole, 2014). An abnormal result of a TTT in this view does not provide a certain diagnosis of VVS, but instead signifies a tendency towards hypotension that becomes manifest in the upright position. This susceptibility may explain why the TTT can be positive in some patients with diverse disorders, including emotional VVS and some forms of cardiac syncope that involve hypotension. The theory assumes that any tendency towards hypotension may become activated in the upright position and result in VVS.

Although a recent paper voiced the opinion that TTT is not of value in the diagnosis of VVS (Kulkarni et al., 2020), this contradicted both European and North American evidence-based syncope guidelines (Brignole et al., 2018a, 2018b; Shen et al., 2017). A response (Sutton et al., 2021) made the point that TTT improved syncope care. A recent European guideline stressed that the diagnostic value of TTT for VVS could be improved by comparing complaints during TTT with those during spontaneous events (Thijs et al., 2021).

2.2.2. Quantifying VD and CI

In the following sections we will show that orthostatic VVS starts with VD, followed by a combination of VD and CI. When VD and CI together lower BP, it was not obvious how much each contributes to the BP decrease (Saal et al., 2017). Under such circumstances, conclusions regarding their relative importance could only be drawn under rare circumstances, such as when there was no HR decrease at all. Another example of such a circumstance was when asystole starts after the onset of LOC (Saal et al., 2017). This 'late asystole' is discussed in Section

2.2.3.

A novel way to quantify the relative changes of VD and CI in orthostatic VVS has been described: the 'log-ratio method' (Van Dijk et al., 2020b). The method is based on the physiological multiplicative equation BP = HR·SV·TPR. It rests on defining periods of interest and calculating one value per patient per period for mean arterial pressure (MAP), HR, SV and TPR. The following step expressed the value of a patient's parameter for one period, say near syncope, as a ratio of that of the baseline period. The chosen baseline was a period shortly after head-up tilt, and therefore reflected the early upright position, in which the VVS process has not yet gained weight; any later hemodynamic changes therefore reflected orthostatic VVS only, not the upright position itself.

The resulting ratios still follow the physiological relation $BP_R = HR_R \cdot SV_R \cdot TPR_R$. They are dimensionless, allowing parameters expressed in different units (for instance L for SV and mmHg·min $\cdot L^{-1}$ for TPR) to be compared directly. The next step was based on the multiplicative nature of the relation and the need to provide groupwise summaries. If three ratios are $HR_R = 0.5$, $SV_R = 2.0$ and $TPR_R = 1.0$, then BP will not have changed. In another person, with $HR_R = 2.0$, $SV_R = 0.5$ and $TPR_R = 1.0$, BP will also not have changed. Simply taking the mean of the ratios would result in 1.25 for both HR and SV, suggesting a nonexistent BP increase. Taking the logarithms of the ratios prevented such errors, and transformed the relation into an additive one: $BP_{LR} = HR_{LR} + SV_{LR} + TPR_{LR}$.

This log-ratio method allowed the relative influences of changes of HR, SV and TPR on BP to be assessed quantitatively over time, between groups, in VVS and in other conditions. While doing justice to the underlying multiplicative physiological relation. This method showed that, a slow decrease of SV was the first observed change in 163 patients with tilt-evoked VVS. It occurred in some subjects as early as nine minutes before syncope (Van Dijk et al., 2020b, Fig. 2). This slow decrease was initially accompanied by a corrective increase of HR with incomplete success, as BP still decreased slowly. TPR did not change significantly in this time (Fig. 3).

At a median time of 58 s before LOC, HR started to decrease in 91% of patients, as evidence of the onset of CI. From then on, HR plummeted, and just before syncope the contribution of low HR to low BP was as large as that of the much slower decrease of SV. There also was a moderate decrease of TPR, adding very little of the effects of SV and HR (Fig. 4). The decrease of SV was explained through a gradual increase of venous pooling that slowly eroded venous return. The authors proposed to expand the concept VD to encompass both venous VD, apparent as a decrease of SV in orthostatic VVS, and arterial VD, apparent through a decrease of TPR. In effect, VD was defined as all processes in reflex syncope that lower BP in other ways than through low HR.

The initial decrease of SV was in agreement with events summarized in a review (Jardine et al., 2018). However, that review stated that TPR tended to rise, perhaps less so in VVS patients. The reason for the difference is probably that the baseline period in several reviewed papers was the supine condition before head-up tilt, whereas the baseline in the

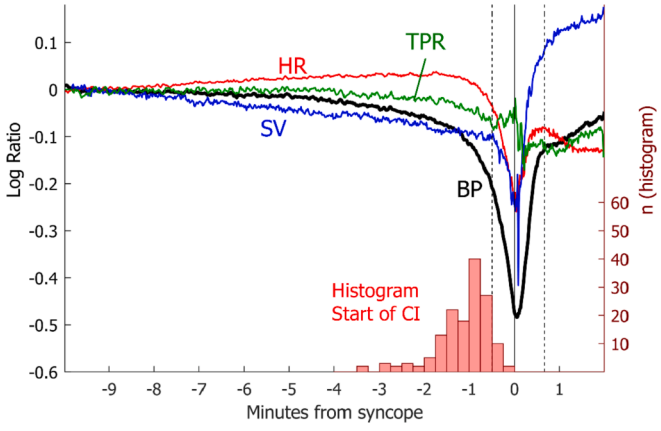

Fig. 2. Hemodynamic features of orthostatic VVS.
The figure is adapted from Van Dijk et al., 2020b. See the main text for a description. The hemodynamic parameters BP, HR, SV and TPR are relative to a baseline period shortly after head-up tilt. The lines represent averages of log-ratio values of 163 persons with tilt-induced VVS. The log-ratio values imply that BP is the sum of the vales of HR, SV and TPR at each instant.
The earliest abnormality of orthostatic VVS is a decrease of SV about 9 min before syncope, due to venous pooling: this represents venous vasodepression. This has the effect of decreasing BP, which is tempered by an increase of HR. About 1 min before syncope, cardioinhibition (CI) starts in the form of an HR decrease. The histogram of the start of CI shows that its onset is variable. The median value was 58 s before syncope. CI causes an acceleration of the BP fall, ending in syncope. While CI is active, there is a modest additional decrease of TPR, adding arterial vasodepression to the much stronger effects of venous VD and CI.

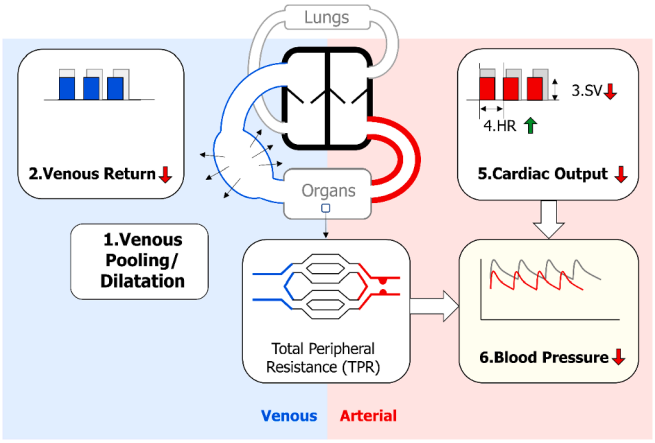

Fig. 3. Overview of the presumed pathophysiological cascade in VVS before the onset of CI.
The abnormalities of orthostatic VVS start with venous pooling (1), here shown as venous vasodilatation. The volume of blood returning to the heart decreases (2), directly translated into a decrease of SV (3). This is partially compensated for by an increase of HR (4), but not enough, so CO decreases (5). In this phase TPR does not change, and BP decreases (6). The typical BP pattern is that systolic BP decreases more than diastolic BP.

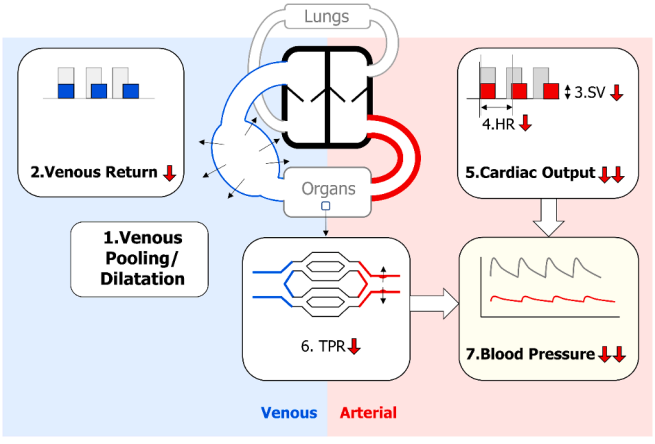

Fig. 4. Overview of the presumed pathophysiological cascade in VVS after the onset of CI.
Continued venous pooling (1) leads to a stronger decrease of venous return (2) and a stronger decrease of SV (3). Now, however, HR decreases (4), so CO decreases more than before (5). Concurrent with the decrease of HR, TPR also decreases slightly (6), so BP reflects the combined influences of decreasing SV, HR and TPR (7). Bp decrease more than before, again with a larger decrease of systolic than diastolic BP.

log ratio paper concerned the early upright condition. If the supine position is used as baseline, hemodynamic changes in the upright condition will consist of responses to head-up tilt itself, typically involving a TPR increase, as well as to the VVS process proper, in which a slight TPR decrease is more likely.

2.2.3. Expanding the role of CI: 'late asystole'

As said, few conclusions could be drawn about the relative importance of CI and VD when both occurred together. Even so, one combination of events allowed an unequivocal conclusion about the role of cardioinhibition, although this was limited to asystole (Saal et al., 2017): asystole cannot be the primary cause of LOC if it starts when patients are already unconscious. In a TTT study using video-EEG to assess LOC, asystole starting 3 s before the onset of LOC or later was considered to not be the primary cause of LOC. The 3 s threshold was based on the earliest interval of 4 s described in Section 2.1.2. This 'late asystole' occurred in one third of the study group, with consequences for cardiac pacing: conventional back-up pacing, in which pacing starts when HR drops below 50 or 60 bpm, might not prevent LOC in one third of cases with asystole.

It may not be assumed that asystole in those with 'early asystole', i.e. asystole starting earlier than 3 s before the onset of LOC, must be the prime mechanism of LOC. Firstly, the 3 s threshold was very conservative, so more than one third of cases may well fall in the 'late asystole' group. Secondly, and more importantly, LOC in those with early asystole was not due to CI only, but to a mixture of CI and VD, as exemplified by low MAP values at the start of asystole

These results showed that the time course of VD and CI differed between patients, with as yet mostly unexplored consequences. The existence of late asystole underlines that documenting HR only provides a very uncertain basis on which to base pacing decisions in orthostatic VVS. Adding a posture detection device to implantable loop recorders might at least detect those in whom asystole starts after a fall: in such persons, asystole-based pacing would be futile.

By its nature, late asystole occurs late in the VVS process (Van Dijk et al., 2020b), so it can only come to light during TTT if the head-up condition lasts long enough to produce complete syncope. This was the case in the log-ratio study (Van Dijk et al., 2020b), as the inclusion criterion was LOC, assessed through video-EEG. However, TTT studies using presyncope as an endpoint are unsuitable to assess the prevalence of asystole, and of that of 'late asystole' in particular.

2.2.4. Expanding the role of CI: not just asystole

CI has been defined as the decrease of HR towards syncope (Van Dijk et al., 2020b), based on a study of 163 patients with complete syncope and a consensus procedure to determine the onset of CI. The examiners were blinded to BP, SV and TPR data. The end of CI was determined as the point of minimum HR around syncope. Measuring both the onset and end of CI allowed its duration, magnitude and speed to be calculated.

In 91% of patients, consensus was reached regarding the point in time at which CI began. This does not mean that HR did not decrease in the remaining 14 patients, just that its onset may have been too slow to allow it to be pinpointed. Magnitude, duration and speed varied considerably between patients.

Aligning the records according to the onset of CI revealed that the already ongoing BP decrease accelerated sharply when CI began, and more so as the speed of CI was higher. CI started when HR was still high, at a mean value of 98 bpm. This high value represented the corrective influence of HR increase. Even the moderate reduction of HR at the start of CI already had a negative impact on BP. HR then continued to decrease to the level needed to maintain the upright condition, and then to its nadir around syncope.

"As said, the onset of CI represents a fundamental change: normal efforts to correct low BP through an increase of HR are abandoned. We suspect that this fundamental change is a consequence of the ongoing vasodepression (Van Dijk et al., 2020a), meaning it is triggered by a circulatory parameter crossing some threshold. In the past, too little filling of the heart was proposed as a trigger, but echocardiography did not reveal the heart to be 'empty' at syncope (Novak et al., 1996; Davrath et al., 1999). One way to indentify the culprit may be to study both the start and end of CI: CI ends at syncope when haemodynamic conditions rapidly normalise, suggesting that CI is maintained as long as a specific condition is fulfilled. Potential factors are haemodynamic or humoral in nature and include wall tension in blood vessels or heart chambers, with perhaps a role for adenosine. Such influences may be modified by how the SA-node integrates incoming signals to form HR."

The demonstrated importance of the corrective effects of the HR increase suggests that preventing CI might keep BP relatively high for longer, hopefully allowing patients the time to sit or lie down and to abort the ongoing VVS evolution. Attempts to prevent the effects of CI may require replacing fall-back pacing, i.e. using preset HR of 50 or 60 bpm, with 'early CI pacing', based on sensing the onset of the HR decrease or another parameter changing in the early stages of orthostatic VVS.

2.2.5. Staging VVS

During orthostatic VVS, the parameters BP, HR, SV and TPR can undergo complex changes: for instance, HR first rises, then starts to decrease at the onset of CI, to reach a nadir at syncope, followed by a rise and a temporary maximum (Van Dijk et al., 2020a). Such 'changes of direction' can consist of an increase or a decrease starting either from a stable situation or from a turn. 'Stages' represented periods between changes of direction; during a stage, the hemodynamic state could be described simply, such as 'BP fell, SV fell and HR rose'. The staging system was based on groupwise observations, did not rest on preconceived notions, and was not intended for individual use.

The two most important changes of direction were the onset of the SV decrease and the onset of CI. The beginning of CI marked the point in time where BP and HR both decreased, i.e. when normal baroreceptor control was lost and replaced by a fundamentally different type of control. Hence, the onset of CI was regarded as a fundamental as well as a literal turning point in the evolution of VVS.

2.3. Cerebral perfusion in VVS

Syncope ensues when cerebral perfusion drops below a critical value, and under normal circumstances brain blood flow depends, as holds for any organ, on the pressure difference of arteries and veins allowing blood in and out of the organ, and the resistance in between. In the case of the brain, the main drive forcing blood into the brain is systolic blood pressure (SBP). Three other pressures can impede that flow: the first is intracranial pressure, normally so low it can be ignored; the second is the resistance of brain blood vessels, normally much lower than in other organs, so the brain is even perfused during diastole. The third pressure is venous pressure, again very low under normal circumstances (Van Dijk et al., 2020a). Hence, in the absence of changes in intracranial and venous pressure, the most important factor driving brain perfusion is SBP, with an added role for DBP, in view of the brain's low resistance. The other factors only play a role when intracranial pressure is very high, or when BP is extremely low, such as in syncope. Cerebral blood flow during syncope was reviewed before (Van Dijk et al., 2020a). Suffice it to state that cerebral autoregulation does its best to decrease the brain's resistance to flow when BP drops in VVS, but cannot keep up with the decrease, so ultimately brain perfusion fails (Schondorf et al., 2001).

Cerebral perfusion was conventionally measured with transcranial Doppler, which is accurate and offers a high temporal resolution, but can suffer from thick skull bones and be difficult to measure when patients move. The advent of 'near-infrared spectroscopy', also called 'noninvasive brain oximetry', is less limiting in this respect. A promising finding in VVS was a decrease in cerebral oxygenation, stated to occur when there were no hemodynamic changes yet (Kharraziha et al., 2019;

Bachus et al., 2018). As brain perfusion critically depends on arterial BP and CO, this is an unlikely combination of findings. A first possible explanations is that there were in fact subtle systemic hemodynamic changes that for unknown reasons did not come to light. Another one is a specific impairment of cerebral perfusion, perhaps through hyperventilation, although then systemic effects should be apparent too (see Section 3). Finally, a shortcoming of near-infrared spectroscopy may be to blame: the technique also records extracranial tissue oxygenation (Badenes et al., 2021). It is reasonable to assume that subtle decreases of CO and BP will affect the noncerebral circulation well before the well-protected cerebral circulation is allowed to suffer. More direct comparisons of near-infrared spectroscopy with transcranial ultrasound studies in VVS are required.

An alternative technique that overcomes some problems of transcranial Doppler is to use ultrasound Doppler studies of cerebral arteries in the neck (Yamamoto et al., 2021).

2.4. Influence of age

The relative contributions of CI and VD probably change with age. In toddlers and young children, asystole is very common in VVS. The duration of asystole decreased with age in small children using eyeball pressure, a technique to evoke VVS (Stephenson, 1990). At the other end of the age spectrum, TTT studies suggested that the proportion of those with asystole decreased with advancing age (Schroeder et al., 2011; Numan et al., 2015). A problem with various such studies was that patients may have been tilted back at presyncope, which may have abolished late events in VVS, including CI and asystole. A recent TTT report, using the Italian protocol relying on syncope as the endpoint of TTT, confirmed that the proportion of asystolic VVS responses decreased with age, and also stated that the contribution of VD increased with age (Rivasi et al., 2021). If confirmed, the latter finding shows that ageing in VVS is not just a matter of overall weakening of autonomic control, but involves differential ageing of CI and VD.

3. Respiratory influences

3.1. Interactions between respiration and the circulation

Respiration influences the circulation in several ways. The first is that intrathoracic respiratory pressure changes not only move air in and out of the thorax, but blood as well. This cyclical effect causes respiratory sinus arrhythmia, an expression of vagal HR control. The respiratory pump enhances venous return, an effect that can in fact increase BP, provided hyperventilation is avoided (Thijs et al., 2007; Thijs et al., 2008).

Hyperventilation, through an increase of respiratory frequency, depth, or both, causes CO_2 to be washed out faster than metabolism can replenish it, resulting in hypocapnia. Hypocapnia in principle causes peripheral vasodilatation and cerebral vasoconstriction. The peripheral vasodilatation may cause arterial hypotension, while cerebral vasoconstriction will increase the resistance of the brain to blood flow. Together, these two factors may quicken and worsen an ongoing syncope tendency. Note that there is no evidence that hyperventilation on its own can cause syncope, even though it may feature in textbook lists of causes of syncope.

The actual effects of hyperventilation on the circulation are complex, because the described effects of ventilation on vessel diameter are normally counteracted by the autonomic nervous system. The peripheral vasodilatation caused by hyperventilation is much more apparent when the autonomic nervous system is damaged, such as in neurogenic orthostatic hypotension, because the counteraction is then reduced (Thijs and van Dijk, 2006; Thijs et al., 2007).

The net effect of hyperventilation on a tendency towards syncope will therefore depend on the magnitude of the respiratory pump, on effects on peripheral and cerebral vasoconstriction, and on counter regulation by the autonomic nervous system.

3.2. Respiratory influences in VVS

VVS can be triggered by fear or anxiety, and such emotions independently cause an increase in ventilation. Symptoms of impending VVS may cause anxiety, potentially resulting in a vicious circle. Hence, hyperventilation and VVS will tend to occur together, even without any physiological interaction between the two processes. It is therefore not surprising that there is evidence of increased ventilation during the evolution of orthostatic VVS during TTT (Kurbaan et al., 2000; Norcliffe-Kaufmann et al., 2008).

However, the effects of respiration on the circulation may be stronger in VVS patients than in controls: voluntary hyperventilation resulted in a greater reduction of peripheral resistance and of cerebral perfusion in patients with VVS than in healthy controls. (Norcliffe-Kaufmann et al., 2008) meaning the stronger response of VVS to hyperventilation may increase the tendency to develop VVS.

People who reported being prone to VVS-like dizziness exhibited more hypocapnia when viewing a surgery video than controls, suggesting that VVS patients have a stronger tendency to respond with anxiety-induced hyperventilation (Harrison et al., 2017). In blood donors, those with more anxiety before donation had larger CO_2 decreases during donation, and larger CO_2 changes were associated with a higher chance of needing treatment for a reaction during donation (Mennitto et al., 2020). A randomized controlled trial comparing 'anti-hyperventilation' with muscle tensing and with no intervention in blood donors concluded that the 'anti-hyperventilation' therapy, while not lowering end-tidal CO_2, did reduce respiratory frequency. Those with little fear of medical situations responded the most (Mennitto et al., 2019).

Hence, all steps in the cascade from anxiety, through hyperventilation and ending with the circulation appear to be enacted stronger in VVS patients than in controls, so this cascade will promote VVS once started. It is possible that the self-reinforcing cascade can start at any point in the emotional, respiratory and circulatory feedback loop.

4. Autonomic control

4.1. Heart rate variability in VVS

Heart rate variability (HRV) is a tool to try to distinguish between sympathetic and parasympathetic influences on HR. As both branches of the autonomic nervous system influence HR, it is inherently difficult to disentangle their effects. HRV efforts to do so largely rely on the two branches responding to different triggers and operating on different time scales. For instance, HR responses to respiration are mostly dependent of parasympathetic control; in a Fourier analysis, these are apparent as the so-called high-frequency peak, whereas sympathetic influences operate at a lower frequency.

Various difficulties have emerged regarding the application of HRV results. A major difficulty is controlling for respiration: HRV is most reliable when BP, HR and in particular respiration are stationary for periods of up to 5 min (Penttilä et al., 2005; Ernst, 2017). All three however change considerably during TTT. As said, many patients hyperventilate, so their respiration changes in depth and frequency. This must alter the high frequency peak, which is then not a reliable indicator of vagal tone. HRV studies during tilt-evoked VVS should therefore attempt to control for rapid respiratory changes.

Many HRV measures depend strongly on mean HR (Monfredi et al., 2014; De Geus et al., 2019; Boyett et al., 2019). Some authors even stated that HRV is just a proxy for HR (Boyett et al., 2019). Unfortunately, how to account for baseline HR is far from settled (Monfredi et al., 2014; De Geus et al., 2019).

HRV analyses can provide pathophysiological insights, in particular when coupled with other approaches such as microneurography. The decrease of baroreceptor control in VVS, described above, differed

between the autonomic branches: cardiac baroreflex gain decreased while sympathetic baroreceptor modulation was virtually abolished (Furlan et al., 2019).

There have been attempts to use HRV analyses to predict the outcome of TTT and through this to improve the diagnosis of VVS, with variable degrees of success (Ciliberti et al., 2018; Klemenc and Štrumbelj, 2015; Miranda and Silva, 2016; Zheng et al., 2020).

A variety of novel HRV methods have been developed and applied to VVS. Examples are very low frequency HR variation (Ciliberti et al., 2018), HR asymmetry (Pawłowski et al., 2021), the cardiac deceleration capacity (Zheng et al., 2020) and self-organized criticality using Zipf's law (Fortrat, 2020). Their clinical value in most cases awaits reproduction.

4.2. Parasympathetic receptors

Beutelstetter and colleagues sought for expressions of vagal overactivity in patients with 'reflex syncope', which presumably concerned VVS (Beutelstetter et al., 2019). The authors reported overexpression of muscarinic M2 receptors in the blood of both adults and children compared to controls. In these patients, acetylcholinesterase expression was also increased. In adults, M2 expression and acetylcholinesterase expression were more pronounced in those who had a positive response to carotid sinus massage. Blood samples were not taken close to a VVS spell, which might be useful for the suggested use as a biomarker (Beutelstetter et al., 2019).

4.3. Role of the baroreflex in VVS

As stated above, HR and BP decrease together in VVS once CI has started, signifying an absence of normal baroreflex control. However, the baroreflex might also act abnormally in VVS patients at rest, or in an earlier phase before CI starts, when BP decreases slowly due to VD. The activity of the baroreflex is usually assessed by measuring how much the RR-interval, the inverse of HR, changes for a given change of BP. The result, baroreflex gain or sensitivity, is expressed as ms per mmHg. Note that this assessment only assesses the parasympathetic effector part of the reflex acting on HR, not the sympathetic part causing vasoconstriction. The amount of vasoconstrictor nerve impulses can be measured using 'microneurographic sympathetic nerve activity'. Recent developments allow an assessment of how much vasoconstriction these impulses represent (Hissen and Taylor, 2020).

A brief review of the baroreflex in VVS (Chaddha et al., 2016) showed contradictory results for baroreflex gain in VVS: some studies showed decreases, others increases or no changes (Chaddha et al., 2016). The conflicting results were attributed to differences in methods or patients groups.

5. Humoral factors in VVS

5.1. Hormones

Benditt et al. reviewed the role of neurohormones in VVS recently (Benditt et al., 2020). Hormonal effects were usually tested in the context of TTT, i.e. orthostatic VVS. Unfortunately, high cost and other reasons make it difficult to obtain multiple blood samples at a high temporal resolution. This means that data are yet lacking to study interactions with the quickly changing hemodynamic situation in VVS.

During presyncope of orthostatic VVS, adrenalin concentration increased considerably, while noradrenalin levels stayed unaltered or increased very little. Near syncope, adrenalin levels were 6 to 15 times higher than at baseline. (Benditt et al., 2020) In other words, the ratio of adrenalin to noradrenalin levels increased, and high ratios proved to associated with a shorter latency to syncope (Kohno et al., 2019; Torabi et al., 2019). When the adrenalin concentration is higher than the noradrenalin one, vasodilatation may occur in some muscle vascular beds. This may contribute to venous pooling in orthostatic VVS. For other hormones we refer to the review (Benditt et al., 2020).

An unsolved problem with these hormonal changes is that it is unclear whether they represent a compensatory effort for aberrant autonomic control, whether they are part of the problem, or both at different times.

5.2. Low-adenosine syncope

As the time of writing, it was not entirely clear whether this type of syncope should be classified as a type of reflex syncope. However, it may well overlap with VVS (Brignole et al., 2020). Adenosin causes bradycardia though A1 receptor stimulation and vasodilatation through A2 receptor stimulation, so its actions fit well with known mechanisms of reflex syncope (Brignole et al., 2020). The clinical characteristics of syncope in patients with low adenosine were viewed recently (Brignole et al., 2020). In short, this type of syncope is characterized by a sudden start of syncope, no prodromes or prodromes of less than 5 s' duration and no cardiac abnormalities (Brignole et al., 2020; Guieu et al., 2020; Deharo et al., 2013; Deharo et al., 2021; Brignole et al., 2017). Compared to typical VVS cases, the low-adenosine patients are generally over 40 years of age; a TTT tends to be negative and the history of syncope is short. (Brignole et al., 2020; Deharo et al., 2013). During syncope these patients have a sudden-onset AV-block or sinus arrest, without the progressive preceding bradycardia commonly seen in VVS (Brignole et al., 2017). The AV-block does not evolve into a permanent AV-block (Blanc and Le Dauphin, 2014).

While typical VVS patients have a purinergic biochemical profile with high adenosine levels, low-adenosine patients have the opposite pattern. Adenosine is normally released during hypoxia, ischemia, beta-adrenergic stimulation and inflammation (Guieu et al., 2020). Adenosine causes a slowing of HR, coronary vasodilatation and a lowering of BP (Guieu et al., 2020). When adenosine plasma levels are low, adenosine mainly affects A1 receptors in the sino-atrial and atrioventricular nodes. The low adenosine levels increase the sensitivity of these receptors, so a temporary adenosine increase can cause a profound bradycardia or AV-block (Brignole et al., 2020).

Unfortunately, the pathophysiology of this type of syncope is not yet clear. Whether the sinus arrest or AV-block syncope is triggered or not, and if so, by which triggers, is at present unknown (Brignole personal communication).

Recognition of the low-adenosine type may allow a better differential diagnosis of the various causes of AV-block and may also have therapeutic consequences, as theophylline should reduce syncope frequency in these patients (Brignole et al., 2019). However, putting this into practice requires the widespread ability to measure adenosine, which is not yet the case.

Adenosine may also affect TTT procedures as it acts faster than nitroglycerine (Kirsch et al., 2007; Tajdini et al., 2021). In one study the positivity rate of TTT did not differ from that of nitroglycerine (Tajdini et al., 2021), and in another it was lower (Kirsch et al., 2007).

5.3. Iron deficiency in 'breath holding spells'

'Breath-holding spells' (BHS) may not be commonly regarded as VVS, but the facts that 'pallid BHS' is triggered by unpleasant stimuli and is characterized by severe cardioinhibition, without a strong respiratory role, shows that its basic features are identical to those of VVS. Unfortunately, the use of multiple names such as 'reflex anoxic seizures' contributes to confusion (Stephenson, 2001). The cyanotic type depends on respiration stopping in expiration (Breningstall, 1996), with circulatory effects occurring secondarily to respiratory ones; as such, cyanotic BHS appear to have no adult counterpart. In spite of these pathophysiological differences, the two types can coexist in a child, and in much of the literature the types are not distinguished. Unfortunately, pathophysiological studies similar to earlier cardinal ones (Stephenson, 1990)

seem to have stopped.

Low iron levels, with or without anemia, were repeatedly reported in BHS (Azab et al., 2015). A meta-analysis of iron supplementation to patients with BHS and iron deficiency showed that supplementation reduced the frequency of spells (Hecht et al., 2020). The authors stressed that the treatment effect depended on iron deficiency, not on anemia. There are reports of low iron levels in older children with VVS as well (Guven et al., 2013; Li et al., 2013), but no reports on iron metabolism in adults with VVS were found.

5.4. Low vitamin D

Two studies reported low vitamin D levels in patients with VVS compared to controls. The first observations concerned 75 adults with VVS and 52 controls; reasons to test vitamin D were not mentioned (Usalp et al., 2020). The result was reproduced in 75 children and adolescents with VVS compared to 15 controls (Zhang et al., 2021). Its functional role is, however, yet unclear.

6. Psychological aspects

6.1. Emotional triggering of VVS

As explained before, the afferent pathway and the early efferent pathway of emotional VVS are essentially unknown. It is clear that the final efferent pathway, with profound hypotension and CI, is the same as in orthostatic VVS. However, lacking a protocol that elicits emotional VVS without any gravitational challenge, it is unknown what happens in emotional VVS before CI is triggered. Clinical experience shows that asystolic emotional VVS may well occur in susceptible patients who undergo medical procedures in the supine position, proving that gravitational stress is certainly not an absolute requirement for VVS. The open question is whether the early phase of emotional VVS resembles the one of orthostatic VVS, with venous pooling and low SV.

Fear and anxiety as triggers of VVS have been abundantly studied in the context of blood donation. For example, donors who were fearful of having a venipuncture were more likely have a vasovagal reaction than those who did not. Of interest, asking about such fears did not increase the risk of such a reaction (France et al., 2019)

Clinical experience also suggest that anxiety need not only act as a precipitating direct trigger of emotional VVS, but can also act as a predisposing factor over a longer timescale. This is supported by an association of childhood sexual and physical abuse with syncope frequency (O'Hare et al., 2017)

6.2. Psychological and psychiatric comorbidity in VVS

Russo et al. investigated personality traits in VVS, because personality was known to modulate an individual's sensitivity to stress, and VVS was known to respond to emotional arousal and uncertainty (Russo et al., 2017). VVS patients indeed proved to be more sensitive to stressors and adapted less quickly to stress. This study is important in that temperament and personality are considered to be fairly stable over long terms, so they should not reflect temporary stressors only.

Other studies reported more anxiety, anxiety sensitivity and depression in VVS patients (Ng et al., 2019; Atici et al., 2020). Childhood physical or sexual abuse was associated with a higher syncope frequency in childhood, and may contribute to a lifelong VVS tendency (O'Hare et al., 2017). While these psychological factors contributed to low quality of life (Ng et al., 2019), it was impossible to determine whether anxiety was the cause or the consequence of VVS, or whether they reinforced one another, with VVS increasing anxiety, and anxiety increasing the VVS tendency. Whether such a positive feedback loop, operating on a time scale of weeks or months, exists for VVS cannot be determined. However, it does exist on the time scale of minutes: the so-called ‘status vasovagalis’ in which VVS in a medical situation precipitates another VVS spell, is evidence of such positive feedback (Thijs et al., 2009).

7. Short summaries and unanswered questions

7.1. Hemodynamic questions

Recent hemodynamic advances allowed a quantification of the relative impact of CI, arterial and venous VD (Van Dijk et al., 2020b).

Clearly, VVS does not occur every time that patients with orthostatic VVS stand for a long time. What is not clear is whether the primary problem is whether a tendency towards venous pooling can become so strong that it cannot be corrected by normal autonomic and hormonal regulation, or whether these corrected efforts are at times too weak to correct normal fluctuations. It is likely that such questions can only be answered if and when a practical and reliable measurement of ongoing venous pooling becomes available.

In either case, it may be wondered whether the venous pooling that initiates the orthostatic VVS cascade should be considered part of a reflex. One would expect that the degree of venous pooling is under autonomic control; if so, the apparent inability to prevent pooling spiraling out of control resembles autonomic failure, or ‘decompensation’, rather than an overactive reflex. In this scenario, the reflex part of VVS only starts with the onset of CI.

CI was redefined as the decrease of HR towards syncope (Van Dijk et al., 2020b). The start of CI consisted of a moderate reduction of the ongoing corrective high HR, and even this resulted in an immediate acceleration of the ongoing BP decrease. These findings, together with the concept of ‘late asystole’, suggest that attempts to prevent LOC in VVS with conventional back-up pacing are likely to fail in an uncomfortably large proportion of cases. Back-up pacing merely sets HR to a threshold value (e.g. 50 or 60 bpm) when spontaneous HR drops below that threshold. When HR reaches that threshold in VVS, VD may already have caused such a large BP decrease that LOC is difficult to prevent. Back-up pacing may likely work well only in those in whom asystole occurs when BP is still high at the onset of asystole. Such hemodynamic considerations suggest that pacing may work much better in orthostatic VVS if two alterations are made: firstly, pacing might start early, at the onset of CI, and the rate should perhaps be high and near the rate at which CI starts, meaning at 90–100 bpm. Such ‘early high-rate pacing’ might in effect abolish the hemodynamic effects of CI.

The contributions of VD, venous and arterial CI may well be different in other causes of reflex syncope, or indeed differ within VVS. In fact, the large variability of changes of HR, SV and TPR may hide as yet undiscovered different hemodynamic patterns. Types of reflex syncope with a very quick onset, such as carotid sinus syncope, are unlikely to start with slow venous pooling, and may represent the presumed ‘classical’ reflex type, with CI and arterial VD only.

There is definitely room to improve measurements of cerebral perfusion in VVS. As discussed above, measuring brain oximetry holds promise, once the problem of possible contamination extracranial tissue oxygenation is solved and comparisons with transcranial Doppler will have been performed.

7.2. Respiratory questions

Anxiety, hyperventilation and its circulatory effects reinforce one another in VVS patients, so their combined effects appear geared to promote VVS. While increased respiratory movements help increase venous return and increases BP, the resulting hypocapnia causes vasodilatation as well as an increase of sympathetic outflow. Hence, the net impact on BP is uncertain. We suspect that the hemodynamic consequences of hyperventilation on VVS are underestimated, possibly because measurements of respiration, such as end-tidal CO_2, are not an integer part of TTT measurements. However, they can be added easily (Thijs et al., 2021), which should provide a basis to determine the net

contribution of respiration to VVS.

7.3. Autonomic questions

Some of the efforts to predict the outcome of TTT using HRV measures might be able to shed light on autonomic control during VVS, if reproduced.

7.4. Humoral questions

Clarifying the real role of hormones in VVS, i.e. whether they are they part of the cause or part of the effect, may well require determining hormonal levels at fairly high temporal resolution, together with hemodynamic assessments. The novel low-adenosine type of syncope shows that humoral factors may be very important in VVS and associated types of syncope, giving rise to the concept of 'neurohumoral' syncope (Brignole et al., 2020). As adenosine can cause both bradycardia and vasodilatation, it may be involved in cardioinhibition as well as in vasodepression.

Whether other metabolic parameters, such as vitamin D or iron levels, will affect clinical practice remains to be seen. However, the subject of 'iron in BHS' provides cause for thought: although there was no strong reason to think that iron would be involved in BHS, characterized as BHS is by a paroxysmal response to external triggers in otherwise healthy infants, there is now a meta-analysis showing that iron supplementation decreases BHS attack frequency (Hecht et al., 2020).

7.5. Psychological questions

The psychology of VVS is obviously of great importance for VVS, but how it affects the hemodynamic state is difficult to assess. This holds in particular for possible long-term influences: does long-term anxiety promote a tendency towards venous pooling, and, if so, through which intermediaries? Both autonomic and hormonal influences may be important here.

However, one psychological pathway can potentially be clarified, and that is how emotional stimuli cause VVS. It should be possible to develop a test for emotional VVS, by eliciting emotional VVS in supine susceptible subjects by showing surgery videos or similar means. A first question would be whether emotional VVS starts with venous pooling as in orthostatic VVS, or whether they proceed directly to pronounced CI and arterial VD. A secondary question might be whether the relatively slow process of anticipation of fearful stimuli promotes venous pooling; if so, sudden unexpected painful or emotional stimuli, such as a fright or stubbing one's toe, might set a different mechanism in motion than anticipating venipuncture.

These questions might have therapeutical consequences: if emotional VVS does not share a slow venous VD phase with orthostatic VVS before CI starts, then the hemodynamic situation with intact venous return should be more amenable to cardiac pacing.

7.6. No more questions?

The most fundamental aspects of VVS are still unknown: how can the sight of blood cause the heart to stop? In orthostatic VVS, why is venous pooling allowed to go unchecked from time to time? Why does HR first increase in an attempt to limit the decrease of BP, and then acts as a 'turncoat', causing BP to plummet?

The overview presented above suggests that answers are more likely to be found when research fields are integrated, which will require cooperation and a broadening of interest to encompass hormone functions, respiration effects as well as psychological factors. Apart from designing directed studies to answer specific questions, much can probably be learned from judicious study of TTT results. Simple means such as adding video recording have led to new insights in the past (van Dijk et al., 2014; Tannemaat et al., 2013; Shmuely et al., 2018), and monitoring more physiological systems, such as respiration, brain perfusion and hormones, are likely to provide additional insights at very low additional cost (Thijs et al., 2021).

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